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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/391,861	09/07/99	THOMASON	A 99.371

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EXAMINER	
STROUP,C	
ART UNIT	**PAPER NUMBER**
1633	12

DATE MAILED: 01/04/01

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/391,861	Applicant(s) THOMASON ET AL.	
	Examiner Carrie Stroup	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13,36, and 39-43* is/are pending in the application.

4a) Of the above claim(s) *6,14-35,37,and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-13,36, and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group I in Paper No. 7 is acknowledged. The traversal is on the ground(s) that Group I, pertaining to polynucleotides, and Group III, pertaining to antibodies are within the same class and are therefore not restrictable because the search for both would not pose an additional burden. This is not found persuasive because even though they are within the same class, they are within different subclasses and require separate search methodologies and considerations for reasons of record in Paper 5, filed 1/27/00, para. "2"). The requirement is still deemed proper and is therefore made FINAL.

Claims 6, 14-35, 37, and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Applicant's amendment in Paper 7 has been entered. Claims 1, 5, 8, 9, and 36 have been amended, and claims 39-43 have been added. Claims 1-5, 7-13, 36, and 39-43 are currently pending.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 1-5, 7-13, 36, and 39-43 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The specification discloses that the claimed sequences were derived via a cloning technique involving the isolation of secreted mammalian growth factors or any peptide which would be expressed in murine liver tissue during cell regeneration using a "signal trap system" (see US Patent 6,150,098- e.g, claim 1; this specification- Example 1, pg 73, lines 7-22). A clone isolated via said system (tmrl 1-00001-e9) was subsequently used as a probe to isolate a full-length cDNA from a mouse liver cDNA library (SEQ ID NO: 3), which the specification discloses displays 32% identity to FGF-6 and 28% identity to FGF-4 (pg 19, lines 20-25). Additionally, a "human FGF-like polypeptide" (SEQ ID NO: 1) was derived by screening a human cDNA library with a probe derived from the murine polypeptide (SEQ ID NO: 3). The two sequences displayed 76% identity (pg 79, line 21).

The specification fails to disclose any functional assay demonstrating the asserted FGF like activity of the claimed sequences. It is widely known in the art that fibroblast growth factors (FGFs) are members of a protein family which has demonstrated a broad range of biological activities involving cell growth and differentiation, such as angiogenesis, morphogenesis, and wound healing (see Faham et al, pg 578, col. 1-2). In the absence of data demonstrating the specific biological function of the polypeptides encoded by the polynucleotides of SEQ ID NO: 1 and 3, then the claimed invention lacks a specific, well-established, and credible utility. Therefore, there is also no established utility for the claimed polynucleotides, vectors, and host cells, or a process for determining whether a compound inhibits FGF-like polypeptide activity or production, or a method of recombinantly producing the claimed sequences, or a method of modulating levels of polypeptide in an animal.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claimed invention is to an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide that is at least about 80% identical to the polypeptide of SEQ ID NO: 2 or 4, and possessing the same activity as such, or serves as an antigen for generating antibodies; allelic and splice variants of SEQ ID NO: 1 or 3, or the unspecified ATCC; a nucleotide sequence encoding a polypeptide fragment of at least 25 amino acid residues with the activity of the polypeptide of SEQ ID NO: 2 or 4 or able to generate antibodies; a fragment of nucleotide sequences SEQ ID NO: 1 or 3 of at least 16 nucleotides; and a nucleotide sequence which hybridizes to and exhibits the activity of or is complementary to any of the above stated nucleic acid sequences (claim 39). The claimed invention is also to a nucleotide sequence encoding a polypeptide of SEQ ID NO: 2 or 4, with at least one conservative amino acid substitution, insertion, deletion, C-terminal and/or N-terminal truncation (claim 40).

As previously stated on the preceding page of this action, the specification fails to disclose any functional assay demonstrating the asserted FGF like activity of the claimed sequences, nor does the specification indicate what distinguishing feature are shared by members of the claimed genus of 80% identical sequences, variants, and fragments of the human and murine FGF-like nucleotide sequences. Thus, the scope of the claims include numerous structural variants, wherein the genus is highly variant because a significant number of structural differences between

genus members is permitted, yet the specification does not provide guidance as to specific nucleotide changes to make. Structural features that could distinquish FGF-like nucleotides demonstrating FGF-like polypeptide activity are missing from the disclosure, as well as a credible assertion of the biological activity of SEQ ID NO: 2 or 4. Therefore, the functional limitation of exhibiting "FGF-like polypeptide activity" is insufficient to describe the genus of variants, homologous sequences, and fragments. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, the applicant was not is possession of the claimed genus.

5. Claims 1-5, 7-13, 36, and 39-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claimed invention is to an isolated nucleic acid molecule comprising the sequence of SEQ ID NO: 1, 2, 3, or 4, or encoding a polypeptide with 80% identity to SEQ ID NO: 2 or 4, or the nucleotide sequence of the DNA insert of an unspecified ATCC Deposit No., or allelic and splice variants and fragments of said sequences, as well as a vector and host cell comprising said nucleic acid, and the method of making a fibroblast growth factor like polypeptide culturing said cell (claims 1-5, 13, 39-43). The claimed invention also includes a nucleic acid molecule comprising SEQ ID NO: 1, 2, 3, or 4, wherein the promoter is heterologous to the FGF-like polypeptide (claim 7); a process for determining whether a compound inhibits FGF-like polypeptide activity by exposing a cell expressing said polypeptide and measuring FGF activity or production (claim 12); and a method of modulating levels of a polypeptide in an animal via administering SEQ ID NO: 1 or 3 as per claim 1 (claim 36).

As pertains to claim 1(c), neither the specification nor the pending claim disclose an ATCC Deposit number (specification, pg 71, lines 23-26). If in fact a deposit has been made under the terms of the Budapest Treaty, then an

affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cDNA has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein under 37 CFR 1.808.

If one the other hand the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.808, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing the following:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer.

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced if it should ever become inviable.

As previously stated in the preceding sections of this action, the specification fails to disclose the specific biological function of the claimed sequences encoded by SEQ ID NO: 1 or 3. Said sequences also display a low sequence identity (32% identity to FGF-6 and 28% identity to FGF-4 (pg 19, lines 20-25)) to two members of the FGF family proteins, a family which is renowned for its divergent in biological functionality. Therefore, the skilled artisan would not known how to use the claimed sequences, or their variants or homologous sequences. Neither could the artisan test for compounds which inhibit FGF-like polypeptide activity by exposing a cell expressing said polypeptide

and measuring FGF activity or production, because the artisan would not known what activity to measure, therefore an evaluation of a compounds ability to inhibit said activity would not be feasible.

Lastly, the specification fails to provide an enabling disclosure for a method of modulating levels of a polypeptide in an animal via administering SEQ ID NO: 1 or 3 as per claim 1 (claim 36). The claim reads on the ability to increase or decrease the level of expression of any endogenous gene or polypeptide in vivo by the interaction of nucleotide sequences encoded by SEQ ID NO: 1 or 3 with said gene (e.g, antisense or homologous recombination), or the interaction of the polypeptide encoded by SEQ ID NO: 2 or 4 following in vivo expression with said polypeptide (e.g, antibody). The claim also reads on the increase in the levels of the polypeptide encoded by SEQ ID NO: 2 or 4 via gene therapy in which SEQ ID NO: 1 or 3 are expressed *in vivo*. It is noted that the specification fails to provide an enabling disclosure for the any of these stated methods, even in the event that the applicant is able to demonstrate a credible utility for the claimed sequences such that the artisan would known how to use said sequences. For example, the specification provides no specific oligonucleotide sequence which may function effectively as antisense to inhibit gene expression in vivo, or specific teachings on methods of conducting gene therapy. It is noted that the teachings disclosed on pages 65-70 pertaining to ex vivo and in vivo gene therapy are general in nature and do not provide essential details, such as specific construct designs to include regulatory sequences, doses per route of administration or methods of assaying for such because the activity of the sequences are not known, or appropriate subjects which would warrant administration of a vector encoding the claimed sequences.

The applicant is reminded that both antisense therapy and gene therapy are highly unpredictable arts. For example, different agonists and antagonists, be it antisense oligonucleotides or antibodies, will have different levels of bioavailability, activity and efficacy in affecting expression of polypeptides because of their different mechanisms of action. Additionally, Branch et al teach in TIBS 23, February 1998, that the use antisense oligonucleotides results in unpredictable outcomes because they often bind to molecules which are not the intended target causing undesirable

side effects in vivo (pg 45, col. 2) and because few sequences are actually able to stably bind *in vivo* to the targeted RNA (pg 49, col. 1).

Likewise, gene therapy, especially in vivo gene therapy, is a highly unpredictable art largely because there are barriers to the *in vivo* delivery of DNA such as: " (1) the rapid degradation of DNA within tissues or blood by nuclease; (ii) the limited dispersion of DNA from the site of interstitial administration; (iii) the inability of DNA to cross intact basement membranes of the endothelium or epithelium effectively; (iv) the rapid clearance of DNA from the vascular compartment by cells of the reticuloendothelial system; (v) the need for effective interaction with the surface of the target cell to induce internalization; (vi) destruction of DNA in the endosomal/lysosomal compartments by nuclease, acid and/or reducing agents; and (vii) the need to penetrate to the nucleus of cells across the periplasmic membrane and nuclear membrane.". (Ledley, pg 1603, col 1, para 3-col 2, para 1). The extent of these barriers directly affects the bioavailability and hence the required dose to effectively elicit any useful (e.g., therapeutic) response.

Additionally, an evaluation of the state-of-the-art of gene therapy by Verma and Somia in Nature 1997, vol 387, pages 239-242 concluded that " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged.....But the problems- such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions- remain formidable challenges.....And Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (Abstract, & pg 239, col 1, para 1-2). Therefore, the lack of teachings specific to administering polynucleotides for a defined physiological effect in a technology that is so unpredictable would result in undue experimentation by one of skill in the art to efficaciously utilize.

6. Claims 8, 9, 12, 13, 36, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 is unclear as to the meaning of the phrase "(a) wherein the polypeptide...". Does use of "(a)" intend that the reader incorporate all of the limitations claim 39 (a) into claim 39 (c), which would result in the redundant use of the phrase "wherein the polypeptide has an activity of the polypeptides set forth in either SEQ ID NO: 2 or SEQ ID NO: 4"?

Claim 40(d) is unclear as to the meaning of "C- and/or - terminal" versus "C- and/or N-terminal".

Claims 8, 9, 12, 13, and 36 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Said claims refer to more than one claim in the alternative.

No claims is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM. Questions of pertaining to formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached at (703) 305-4051. The fax number for this Group is (703) 308-0294.

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